

Claims

1. An immunogenic composition comprising two or more different antigens, wherein the antigens are selected from at least two of the following categories:
 - 5 a) at least one Neisserial adhesin;
 - b) at least one Neisserial autotransporter;
 - c) at least one Neisserial toxin;
 - d) at least one Neisserial Fe acquisition protein; or
 - e) at least one Neisserial membrane associated protein, preferably integral outer membrane protein.
- 10
2. The immunogenic composition of claim 1, wherein the antigens are selected from at least two of the following categories:
 - a) at least one Neisserial adhesin selected from the group consisting of FhaB, NspA, PilC, Hsf, Hap, MafA, MafB, Omp26, NMB0315, NMB0995, NMB1119 and NadA;
 - 15 b) at least one Neisserial autotransporter selected from the group consisting of Hsf, Hap, IgA protease, AspA and NadA;
 - c) at least one Neisserial toxin selected from the group consisting of FrpA, FrpC, FrpA/C, VapD, NM-ADPRT, and either or both of LPS immunotype L2 and LPS immunotype L3;
 - 20 d) at least one Neisserial Fe acquisition protein selected from the group consisting of TbpA high, TbpA low, TbpB high, TbpB low, LbpA, LbpB, P2086, HpuA, HpuB, Lipo28, Sibp, FbpA, BfrA, BfrB, Bcp, NMB0964 and NMB0293; or
 - 25 e) at least one Neisserial membrane associated protein, preferably integral outer membrane protein selected from the group consisting of PilQ, OMP85, FhaC, NspA, TbpA(high), TbpA(low), LbpA, HpuB, TspA, TspB, TdfH, PorB, HimD, HisD, GNA1870, OstA, HlpA, MltA, NMB 1124, NMB 1162, NMB 30 1220, NMB 1313, NMB 1953, HtrA and PldA.
3. The immunogenic composition of claim 1 or 2 which is a subunit composition
4. The immunogenic composition of claim 3 comprising at least 2 antigens selected from the following list: FhaB, NspA, passenger domain of Hsf, passenger domain of Hap, surface exposed domain of OMP85, FrpA, FrpC, TbpB, LbpB, PldA, PilC, Lipo28 and either or both of LPS immunotype L2 and LPS immunotype L3.
- 35
5. The immunogenic composition of claim 1 or 2 comprising an outer membrane vesicle preparation, wherein the antigens have been upregulated (preferably recombinantly) in the outer membrane vesicle.
- 40
6. The immunogenic composition of claim 5 comprising at least two antigens selected from the following list which have been upregulated in the outer membrane vesicle: NspA, Hsf, Hap, OMP85, AspA, HpuA, HpuB, TspA, TspB, FhaC, TbpA (high), TbpA (low), LbpA, TbpB, LbpB, PilQ, NM-ADPRT, P2086, TdfH, PorB, MafA, MafB, HimD, HisD, GNA1870, OstA, HlpA, MltA and PldA; and optionally comprising either or both of LPS immunotype L2 and LPS immunotype L3.
- 45
- 50

7. The immunogenic composition of claim 1 or 2 comprising a subunit composition having one or more of the antigens, and an outer membrane vesicle preparation having at least one antigen which has been upregulated in the outer membrane vesicle.
8. The immunogenic composition of claim 7 comprising a subunit composition and an outer membrane vesicle preparation wherein the subunit composition comprises at least one antigen selected from the following list: FhaB, NspA, passenger domain of Hsf, passenger domain of Hap, surface exposed domain of OMP85, FrpA, FrpC, TbpB, LbpB, PilC, Lipo28 and the outer membrane vesicle preparation having at least one different antigen selected from the following list, which has been recombinantly upregulated in the outer membrane vesicle: NspA, Hsf, Hap, OMP85, AspA, HpuA, HpuB, TspA, TspB, FhaC, TbpA (high), TbpA (low), LbpA, TbpB, LbpB, PilQ, NM-ADPRT, P2086, TdfH, PorB, MafA, MafB, HimD, HisD, GNA1870, OstA, HlpA, MltA and PldA; and optionally comprising either or both of LPS immunotype L2 and LPS immunotype L3, preferably within the outer membrane vesicle preparation.
9. The immunogenic composition of claims 5-8 comprising at least two different outer membrane vesicle preparations of claim 5 or 6.
10. The immunogenic composition of claim 9 wherein one outer membrane vesicle preparation is immunotype L2 and one outer membrane vesicle preparation is immunotype L3.
11. The immunogenic composition of claims 1, 2, 5, 6, 7, 8, 9 or 10 wherein Hsf and TbpA (high) are selected.
12. The immunogenic composition of claims 1-2 or 5-11, wherein Hsf and TbpA (low) are selected.
13. The immunogenic composition of claims 11 or 12 wherein one or more additional antigens from a list consisting of Hap, LbpB, OMP 85 and FrpA are further selected.
14. The immunogenic composition of claims 11-13 wherein LPS immunotype L2 is further selected.
15. The immunogenic composition of claims 11-14 wherein LPS immunotype L3 is further selected.
16. The immunogenic composition of claims 1-15 wherein FhaB is selected together with at least one further antigen selected from the group consisting of : PilC, MafA, MafB, Omp26, NMB0995, FhaC, FbpA, Bcp, NMB 1124, NMB 1162, NMB 1220, NMB 1313, NMB 1953, HtrA, Hsf, LbpB, FrpA, FrpC, FrpA/C, NadA, OMP85, PldA, LbpA, TbpA (low), TbpA(high), TbpB(low), TbpB(high), HpuA, HpuB, Hap, IgA protease, AspA, PilQ, MltA, HimD, HisD, GNA1870, OstA, HlpA, NspA, TspA, TspB, P2086, Lipo28, Sibp, NMB0964, NMB0293,

NMB0315, NMB1119, TdfH, PorB, NM-ADPRT, VapD and either or both of LPS immunotype L2 and LPS immunotype L3.

17. The immunogenic composition of claims 1-16 wherein NspA is selected together
5 with at least one further antigen selected from the group consisting of : PilC,
MafA, MafB, Omp26, NMB0995, FhaC, FbpA, Bcp, NMB 1124, NMB 1162,
NMB 1220, NMB 1313, NMB 1953, HtrA, Hsf, LbpB, FrpA, FrpC, FrpA/C,
NadA, OMP85, PldA, LbpA, TbpA (low), TbpA(high), TbpB(low), TbpB(high),
10 HpuA, HpuB, Hap, IgA protease, AspA, PilQ, MltA, HimD, HisD, GNA1870,
OstA, HlpA, TspA, TspB, P2086, Lipo28, Sibp, NMB0964, NMB0293,
NMB0315, NMB1119, TdfH, PorB, NM-ADPRT, VapD and either or both of LPS
immunotype L2 and LPS immunotype L3.

18. The immunogenic composition of claims 1-17 wherein NadA is selected together
15 with at least one further antigen selected from the group consisting of : PilC,
MafA, MafB, Omp26, NMB0995, FhaC, FbpA, Bcp, NMB 1124, NMB 1162,
NMB 1220, NMB 1313, NMB 1953, HtrA, Hsf, LbpB, FrpA, FrpC, FrpA/C,
OMP85, PldA, LbpA, TbpA (low), TbpA(high), TbpB(low), TbpB(high), HpuA,
20 HpuB, Hap, IgA protease, AspA, PilQ, MltA, HimD, HisD, GNA1870, OstA,
HlpA, TspA, TspB, P2086, Lipo28, Sibp, NMB0964, NMB0293, NMB0315,
NMB1119, TdfH, PorB, NM-ADPRT, VapD and either or both of LPS
immunotype L2 and LPS immunotype L3.

19. The immunogenic composition of claims 1-18 wherein TbpA (low) is selected
25 together with at least one further antigen selected from the group consisting of:
PilC, MafA, MafB, Omp26, NMB0995, FhaC, FbpA, Bcp, NMB 1124, NMB
1162, NMB 1220, NMB 1313, NMB 1953, HtrA, Hsf, LbpB, FrpA, FrpC,
FrpA/C, OMP85, PldA, LbpA, TbpA(high), TbpB(low), TbpB(high), HpuA,
HpuB, Hap, IgA protease, AspA, PilQ, MltA, HimD, HisD, GNA1870, OstA,
30 HlpA, TspA, TspB, P2086, Lipo28, Sibp, NMB0964, NMB0293, NMB0315,
NMB1119, TdfH, PorB, NM-ADPRT, VapD and either or both of LPS
immunotype L2 and LPS immunotype L3.

20. The immunogenic composition of claims 1-19 wherein TbpA (high) is selected
35 together with at least one further antigen selected from the group consisting of:
PilC, MafA, MafB, Omp26, NMB0995, FhaC, FbpA, Bcp, NMB 1124, NMB
1162, NMB 1220, NMB 1313, NMB 1953, HtrA, Hsf, LbpB, FrpA, FrpC,
FrpA/C, OMP85, PldA, LbpA, TbpB(low), TbpB(high), HpuA, HpuB, Hap, IgA
40 protease, AspA, PilQ, MltA, HimD, HisD, GNA1870, OstA, HlpA, TspA, TspB,
P2086, Lipo28, Sibp, NMB0964, NMB0293, NMB0315, NMB1119, TdfH,
PorB, NM-ADPRT, VapD and either or both of LPS immunotype L2 and LPS
immunotype L3.

21. The immunogenic composition of claims 1-20 wherein LbpB is selected together
45 with at least one further antigen selected from the group consisting of: PilC,
MafA, MafB, Omp26, NMB0995, FhaC, FbpA, Bcp, NMB 1124, NMB 1162,
NMB 1220, NMB 1313, NMB 1953, HtrA, Hsf, FrpA, FrpC, FrpA/C, OMP85,
PldA, LbpA, TbpB(low), TbpB(high), HpuA, HpuB, Hap, IgA protease, AspA,
PilQ, MltA, HimD, HisD, GNA1870, OstA, HlpA, TspA, TspB, P2086, Lipo28,

Sibp, NMB0964, NMB0293, NMB0315, NMB1119, TdfH, PorB, NM-ADPRT, VapD and either or both of LPS immunotype L2 and LPS immunotype L3.

22. The immunogenic composition of claims 1-21 wherein OMP85 is selected together with at least one further antigen selected from the group consisting of:
5 PilC, MafA, MafB, Omp26, NMB0995, FhaC, FbpA, Bcp, NMB 1124, NMB 1162, NMB 1220, NMB 1313, NMB 1953, HtrA, Hsf, FrpA, FrpC, FrpA/C, PldA, LbpA, TbpB(low), TbpB(high), HpuA, HpuB, Hap, IgA protease, AspA, PilQ, MltA, HimD, HisD, GNA1870, OstA, HlpA, TspA, TspB, P2086, Lipo28, Sibp, NMB0964, NMB0293, NMB0315, NMB1119, TdfH, PorB, NM-ADPRT, VapD and either or both of LPS immunotype L2 and LPS immunotype L3.
23. The immunogenic composition of claims 1-22 wherein Hap is selected together with at least one further antigen selected from the group consisting of: PilC,
10 MafA, MafB, Omp26, NMB0995, FhaC, FbpA, Bcp, NMB 1124, NMB 1162, NMB 1220, NMB 1313, NMB 1953, HtrA, Hsf, FrpA, FrpC, FrpA/C, PldA, LbpA, TbpB(low), TbpB(high), HpuA, HpuB, IgA protease, AspA, PilQ, MltA, 15 HimD, HisD, GNA1870, OstA, HlpA, TspA, TspB, P2086, Lipo28, Sibp, NMB0964, NMB0293, NMB0315, NMB1119, TdfH, PorB, NM-ADPRT, VapD and either or both of LPS immunotype L2 and LPS immunotype L3.
24. The immunogenic composition of claims 1-23 wherein Hsf is selected together
20 with at least one further antigen selected from the group consisting of: PilC, MafA, MafB, Omp26, NMB0995, FhaC, FbpA, Bcp, NMB 1124, NMB 1162, NMB 1220, NMB 1313, NMB 1953, HtrA, FrpA, FrpC, FrpA/C, PldA, LbpA, TbpB(low), TbpB(high), HpuA, HpuB, IgA protease, AspA, PilQ, MltA, 25 HimD, HisD, GNA1870, OstA, HlpA, TspA, TspB, P2086, Lipo28, Sibp, NMB0964, NMB0293, NMB0315, NMB1119, TdfH, PorB, NM-ADPRT, VapD and either or both of LPS immunotype L2 and LPS immunotype L3.
25. The immunogenic composition of claims 1-24 wherein Frp A is selected together
30 with at least one further antigen selected from the group consisting of: PilC, MafA, MafB, Omp26, NMB0995, FhaC, FbpA, Bcp, NMB 1124, NMB 1162, NMB 1220, NMB 1313, NMB 1953, HtrA, FrpC, FrpA/C, PldA, LbpA, TbpB(low), TbpB(high), HpuA, HpuB, IgA protease, AspA, PilQ, MltA, 35 HimD, HisD, GNA1870, OstA, HlpA, TspA, TspB, P2086, Lipo28, Sibp, NMB0964, NMB0293, NMB0315, NMB1119, TdfH, PorB, NM-ADPRT, VapD and either or both of LPS immunotype L2 and LPS immunotype L3.
26. The immunogenic composition of claims 1-25 wherein FrpC is selected together
40 with at least one further antigen selected from the group consisting of: PilC, MafA, MafB, Omp26, NMB0995, FhaC, FbpA, Bcp, NMB 1124, NMB 1162, NMB 1220, NMB 1313, NMB 1953, HtrA, PldA, LbpA, TbpB(low), TbpB(high), HpuA, HpuB, IgA protease, AspA, PilQ, MltA, HimD, HisD,
45 GNA1870, OstA, HlpA, TspA, TspB, P2086, Lipo28, Sibp, NMB0964, NMB0293, NMB0315, NMB1119, TdfH, PorB, NM-ADPRT, VapD and either or both of LPS immunotype L2 and LPS immunotype L3.
27. The immunogenic composition of claims 1-26 wherein LPS immunotype L2 is
50 selected together with at least one further antigen selected from the group

consisting of: PilC, MafA, MafB, Omp26, NMB0995, FhaC, FbpA, Bcp, NMB 1124, NMB 1162, NMB 1220, NMB 1313, NMB 1953, HtrA, PldA, LbpA, TbpB(low), TbpB(high), HpuA, HpuB, IgA protease, AspA, PilQ, MltA, HimD, HisD, GNA1870, OstA, HlpA, TspA, TspB, P2086, Lipo28, Sibp, NMB0964, NMB0293, NMB0315, NMB1119, TdfH, PorB, NM-ADPRT, VapD and LPS immunotype L3.

28. The immunogenic composition of claims 1-27 wherein LPS immunotype L3 is selected together with at least one further antigen selected from the group consisting of: PilC, MafA, MafB, Omp26, NMB0995, FhaC, FbpA, Bcp, NMB 1124, NMB 1162, NMB 1220, NMB 1313, NMB 1953, HtrA, PldA, LbpA, TbpB(low), TbpB(high), HpuA, HpuB, IgA protease, AspA, PilQ, MltA, HimD, HisD, GNA1870, OstA, HlpA, TspA, TspB, P2086, Lipo28, Sibp, NMB0964, NMB0293, NMB0315, NMB1119, TdfH, PorB, NM-ADPRT and VapD.
29. The immunogenic composition of claims 1-28 wherein PilQ is selected together with at least one further antigen selected from the group consisting of: PilC, MafA, MafB, Omp26, NMB0995, FhaC, FbpA, Bcp, NMB 1124, NMB 1162, NMB 1220, NMB 1313, NMB 1953, HtrA, PldA, LbpA, TbpB(low), TbpB(high), HpuA, HpuB, IgA protease, AspA, MltA, HimD, HisD, GNA1870, OstA, HlpA, TspA, TspB, P2086, Lipo28, Sibp, NMB0964, NMB0293, NMB0315, NMB1119, TdfH, PorB, NM-ADPRT and VapD.
30. The immunogenic composition of claims 1-29 wherein HlpA is selected together with at least one further antigen selected from the group consisting of: PilC, MafA, MafB, Omp26, NMB0995, FhaC, FbpA, Bcp, NMB 1124, NMB 1162, NMB 1220, NMB 1313, NMB 1953, HtrA, PldA, LbpA, TbpB(low), TbpB(high), HpuA, HpuB, IgA protease, AspA, MltA, HimD, HisD, GNA1870, OstA, TspA, TspB, P2086, Lipo28, Sibp, NMB0964, NMB0293, NMB0315, NMB1119, TdfH, PorB, NM-ADPRT and VapD.
31. The immunogenic composition of claims 1-30 wherein MltA is selected together with at least one further antigen selected from the group consisting of: PilC, MafA, MafB, Omp26, NMB0995, FhaC, FbpA, Bcp, NMB 1124, NMB 1162, NMB 1220, NMB 1313, NMB 1953, HtrA, PldA, LbpA, TbpB(low), TbpB(high), HpuA, HpuB, IgA protease, AspA, HimD, HisD, GNA1870, OstA, TspA, TspB, P2086, Lipo28, Sibp, NMB0964, NMB0293, NMB0315, NMB1119, TdfH, PorB, NM-ADPRT and VapD.
32. The immunogenic composition of claims 1-31 wherein GNA1870 is selected together with at least one further antigen selected from the group consisting of: PilC, MafA, MafB, Omp26, NMB0995, FhaC, FbpA, Bcp, NMB 1124, NMB 1162, NMB 1220, NMB 1313, NMB 1953, HtrA, PldA, LbpA, TbpB(low), TbpB(high), HpuA, HpuB, IgA protease, AspA, HimD, HisD, OstA, TspA, TspB, P2086, Lipo28, Sibp, NMB0964, NMB0293, NMB0315, NMB1119, TdfH, PorB, NM-ADPRT and VapD.
33. The immunogenic composition of claims 1-32 wherein NM-ADPRT is selected together with at least one further antigen selected from the group consisting of:

PilC, MafA, MafB, Omp26, NMB0995, FhaC, FbpA, Bcp, NMB 1124, NMB 1162, NMB 1220, NMB 1313, NMB 1953, HtrA, PldA, LbpA, TbpB(low), TbpB(high), HpuA, HpuB, IgA protease, AspA, HimD, HisD, OstA, TspA, TspB, P2086, Lipo28, Sibp, NMB0964, NMB0293, NMB0315, NMB1119, TdfH, PorB, and VapD.

5 34. The immunogenic composition of claims 1-33 wherein MafA is selected together with at least one further antigen selected from the group consisting of: PilC, MafB, Omp26, NMB0995, FhaC, FbpA, Bcp, NMB 1124, NMB 1162, NMB 1220, NMB 1313, NMB 1953, HtrA, PldA, LbpA, TbpB(low), TbpB(high), HpuA, HpuB, IgA protease, AspA, HimD, HisD, OstA, TspA, TspB, P2086, Lipo28, Sibp, NMB0964, NMB0293, NMB0315, NMB1119, TdfH, PorB, and VapD.

10 35. The immunogenic composition of claims 1-34 wherein MafB is selected together with at least one further antigen selected from the group consisting of: PilC, MafB, Omp26, NMB0995, FhaC, FbpA, Bcp, NMB 1124, NMB 1162, NMB 1220, NMB 1313, NMB 1953, HtrA, PldA, LbpA, TbpB(low), TbpB(high), HpuA, HpuB, IgA protease, AspA, HimD, HisD, OstA, TspA, TspB, P2086, 20 Lipo28, Sibp, NMB0964, NMB0293, NMB0315, NMB1119, TdfH, PorB, and VapD.

25 36. The immunogenic composition of claims 1-35 wherein NMB0315 is selected together with at least one further antigen selected from the group consisting of: PilC, MafB, Omp26, NMB0995, FhaC, FbpA, Bcp, NMB 1124, NMB 1162, NMB 1220, NMB 1313, NMB 1953, HtrA, PldA, LbpA, TbpB(low), TbpB(high), HpuA, HpuB, IgA protease, AspA, HimD, HisD, OstA, TspA, TspB, P2086, Lipo28, Sibp, NMB0964, NMB0293, NMB1119, TdfH, PorB, and VapD.

30 37. The immunogenic composition of claims 1-36 wherein NMB1119 is selected together with at least one further antigen selected from the group consisting of: PilC, MafB, Omp26, NMB0995, FhaC, FbpA, Bcp, NMB 1124, NMB 1162, NMB 1220, NMB 1313, NMB 1953, HtrA, PldA, LbpA, TbpB(low), TbpB(high), HpuA, HpuB, IgA protease, AspA, HimD, HisD, OstA, TspA, TspB, P2086, 35 Lipo28, Sibp, NMB0964, NMB0293, NMB1119, TdfH, PorB, and VapD.

40 38. The immunogenic composition of claims 1-37 wherein HisD is selected together with at least one further antigen selected from the group consisting of: PilC, MafB, Omp26, NMB0995, FhaC, FbpA, Bcp, NMB 1124, NMB 1162, NMB 1220, NMB 1313, NMB 1953, HtrA, PldA, LbpA, TbpB(low), TbpB(high), HpuA, HpuB, IgA protease, AspA, HimD, OstA, TspA, TspB, P2086, Lipo28, Sibp, NMB0964, NMB0293, NMB1119, TdfH, PorB, and VapD.

45 39. The immunogenic composition of claims 1-38 wherein LbpA is selected together with at least one further antigen selected from the group consisting of: PilC, MafB, Omp26, NMB0995, FhaC, FbpA, Bcp, NMB 1124, NMB 1162, NMB 1220, NMB 1313, NMB 1953, HtrA, PldA, TbpB(low), TbpB(high), HpuA,

HpuB, IgA protease, AspA, HimD, OstA, TspA, TspB, P2086, Lipo28, Sibp, NMB0964, NMB0293, NMB1119, TdfH, PorB, and VapD.

40. The immunogenic composition of claims 1-39 wherein NMB 0995 is selected together with at least one further antigen selected from the group consisting of: PilC, MafB, Omp26, FhaC, FbpA, Bcp, NMB 1124, NMB 1162, NMB 1220, NMB 1313, NMB 1953, HtrA, PldA, TbpB(low), TbpB(high), HpuA, HpuB, IgA protease, AspA, HimD, OstA, TspA, TspB, P2086, Lipo28, Sibp, NMB0964, NMB0293, NMB1119, TdfH, PorB, and VapD.

10 41. The immunogenic composition of claims 1-40 wherein Lipo28 is selected together with at least one further antigen selected from the group consisting of: PilC, MafB, Omp26, FhaC, FbpA, Bcp, NMB 1124, NMB 1162, NMB 1220, NMB 1313, NMB 1953, HtrA, PldA, TbpB(low), TbpB(high), HpuA, HpuB, IgA protease, AspA, HimD, OstA, TspA, TspB, P2086, Sibp, NMB0964, NMB0293, NMB1119, TdfH, PorB, and VapD.

15 42. The immunogenic composition of claims 1-41 wherein HimD is selected together with at least one further antigen selected from the group consisting of: PilC, MafB, Omp26, FhaC, FbpA, Bcp, NMB 1124, NMB 1162, NMB 1220, NMB 1313, NMB 1953, HtrA, PldA, TbpB(low), TbpB(high), HpuA, HpuB, IgA protease, AspA, OstA, TspA, TspB, P2086, Sibp, NMB0964, NMB0293, NMB1119, TdfH, PorB, and VapD.

20 43. The immunogenic composition of claims 1-42 wherein NMB1313 is selected together with at least one further antigen selected from the group consisting of: PilC, MafB, Omp26, FhaC, FbpA, Bcp, NMB 1124, NMB 1162, NMB 1220, NMB 1953, HtrA, PldA, TbpB(low), TbpB(high), HpuA, HpuB, IgA protease, AspA, OstA, TspA, TspB, P2086, Sibp, NMB0964, NMB0293, NMB1119, TdfH, PorB, and VapD.

25 44. The immunogenic composition of claims 1-43 wherein NMB1953 is selected together with at least one further antigen selected from the group consisting of: PilC, MafB, Omp26, FhaC, FbpA, Bcp, NMB 1124, NMB 1162, NMB 1220, HtrA, PldA, TbpB(low), TbpB(high), HpuA, HpuB, IgA protease, AspA, OstA, TspA, TspB, P2086, Sibp, NMB0964, NMB0293, NMB1119, TdfH, PorB, and VapD.

30 45. The immunogenic composition of claims 5-44 wherein a host cell from which the outer membrane vesicle preparation is derived has been engineered so as to down-regulate the expression from one or more of lgtB or lgtE, preferably the former.

35 46. The immunogenic composition of claims 5-45 wherein a host cell from which the outer membrane vesicle preparation is derived is unable to synthesize capsular polysaccharide and has preferably been engineered so as to down-regulate the expression from one or more of siaD, ctrA, ctrB, ctrC, ctrD, synA (equivalent to synX and siaA) or synB (equivalent to siaB and synC (equivalent to siaC), preferably siaD.

47. The immunogenic composition of claims 5-46 wherein a host cell from which the outer membrane vesicle preparation is derived has been engineered so as to down-regulate the expression of one or more of OpC, OpA or PorA, preferably PorA.
- 5 48. The immunogenic composition of claims 5-47 wherein a host cell from which the outer membrane vesicle preparation is derived has been engineered so as to down-regulate the expression of FrpB.
- 10 49. The immunogenic composition of claims 5-48 wherein a host cell from which the outer membrane vesicle preparation is derived has been engineered so as to down-regulate the expression from msbB and/or htrB, preferably msbB.
- 15 50. The immunogenic composition of claims 5-49 wherein the outer membrane vesicle preparation contains LPS which is conjugated to an outer membrane protein (OMP).
- 20 51. The immunogenic composition of claim 50 wherein LPS is conjugated (preferably intra-bleb) to OMP in situ in the outer membrane vesicle preparation.
52. The immunogenic composition of claims 1-51 comprising an antigen derived from *Neisseria meningitidis*, preferably serogroup B.
- 25 53. The immunogenic compositions of claims 1-52 comprising an antigen derived from *Neisseria gonorrhoeae*.
54. The immunogenic composition of claims 1-52 wherein all neisserial antigens are derived from N.meningitidis, preferably serogroup B.
- 30 55. The immunogenic composition of claims 1-54 further comprising one or more bacterial capsular polysaccharides or oligosaccharides.
- 35 56. The immunogenic composition of claim 55 wherein the capsular polysaccharides or oligosaccharides are derived from bacteria selected from the group consisting of: *Neisseria meningitidis* serogroup A, C, Y and W-135, *Haemophilus influenzae* b, *Streptococcus pneumoniae*, Group A Streptococci, Group B Streptococci, *Staphylococcus aureus* and *Staphylococcus epidermidis*.
- 40 57. The immunogenic composition of claims 55-56 wherein the capsular polysaccharide or oligosaccharide is conjugated to a protein.
58. The immunogenic composition of claims 1-57 comprising an adjuvant.
- 45 59. The immunogenic composition of claim 58 comprising aluminium salts, preferably aluminium phosphate.
60. The immunogenic composition of claim 58 or 59 comprising 3D-MPL.

61. A vaccine comprising the immunogenic composition of claims 1-60 and a pharmaceutically acceptable carrier.
62. A vaccine comprising one or more polynucleotide(s) encoding two or more different proteins whose expression is driven by a eukaryotic promoter, wherein the proteins are selected from at least two of the following categories:
 - a) at least one Neisserial adhesin selected from the group consisting of FhaB, NspA, PilC, Hsf, Hap, MafA, MafB, Omp26, NMB0315, NMB0995, NMB1119 and NadA;
 - b) at least one Neisserial autotransporter selected from the group consisting of Hsf, Hap, IgA protease, AspA and NadA;
 - c) at least one Neisserial toxin selected from the group consisting of FrpA, FrpC, FrpA/C, VapD and NM-ADPRT;
 - d) at least one Neisserial Fe acquisition protein selected from the group consisting of TbpA high, TbpA low, TbpB high, TbpB low, LbpA, LbpB, P2086, HpuA, HpuB, Lipo28, Sibp, FbpA, BfrA, BfrB, Bcp, NMB0964 and NMB0293; or
 - e) at least one Neisserial membrane associated protein, preferably integral outer membrane protein selected from the group consisting of PilQ, OMP85, FhaC, NspA, TbpA(high), TbpA(low), LbpA, HpuB, TspA, TspB, TdfH, PorB, HimD, HisD, GNA1870, OstA, HlpA, MltA, NMB 1124, NMB 1162, NMB 1220, NMB 1313, NMB 1953, HtrA and PldA.
63. A method for treatment or prevention of Neisserial disease comprising administering a protective dose of the vaccine of claims 61-62 to a host in need thereof.
64. The method of claim 63 in which *Neisseria meningitidis* infection is prevented or treated.
65. The method of claim 63 in which *Neisseria gonorrhoeae* infection is prevented or treated.
66. A use of the vaccine of claims 61-62 in the preparation of a medicament for treatment or prevention of Neisserial infection.
67. The use of claim 66 in which *Neisseria meningitidis* infection is prevented or treated.
68. The use of claim 66 in which *Neisseria gonorrhoeae* infection is prevented or treated.
69. A genetically engineered Neisserial strain from which the outer membrane vesicle preparation of claims 5-60 is derived.
70. A method of making the immunogenic composition of claim 1-60 comprising a step of mixing together at least two antigens from Neisseria.
71. A method of making the immunogenic composition of claims 5-60 comprising a step of isolating outer membrane vesicles from a Neisserial culture.

72. The method of claim 71 comprising a further step of combining at least two outer membrane vesicle preparations.
- 5 73. The method of claim 72 wherein at least one outer membrane vesicle preparation contains LPS of immunotype L2 and at least one outer membrane vesicle preparation contains LPS of immunotype L3.
- 10 74. The method of claims 71-73 wherein the outer membrane vesicles are isolated by extracting with a concentration of DOC of 0 - 0.5%.
75. The method of claim 74 wherein the outer membrane vesicles are isolated by extracting with a concentration of DOC of 0.02%-0.4%, 0.04%-0.3%, 0.06%-0.2%, 0.08%-0.15% or preferably around or exactly 0.1%.
- 15 76. A method of making the vaccine of claim 61 comprising a step of combining the immunogenic composition of claims 1-60 with a pharmaceutically acceptable carrier.
- 20 77. A method of preparing an immune globulin for use in prevention or treatment of Neisserial infection comprising the steps of immunising a recipient with the vaccine of claim 61 and isolating immune globulin from the recipient.
78. An immune globulin prepared by the method of claim 77.
- 25 79. A pharmaceutical composition comprising the immune globulin of claim 78 and a pharmaceutically acceptable carrier.
80. A method for treatment or prevention of Neisserial infection comprising a step of administering to a patient an effective amount of the pharmaceutical preparation of claim 79.
- 30 81. A use of the pharmaceutical preparation of claim 79 in the manufacture of a medicament for the treatment or prevention of Neisserial disease.
- 35 82. The immunogenic composition of claim 5-60, comprising a meningococcal bleb of immunotype L2 and a meningococcal bleb of immunotype L3.
83. The immunogenic composition of claim 82 wherein TbpA(high) is upregulated in one of the blebs.
- 40 84. The immunogenic composition of claim 82 or 83 wherein TbpA(low) is upregulated in one of the blebs.
85. The immunogenic composition of claims 82-84 wherein Hsf is upregulated in one of the blebs.
- 45 86. The immunogenic composition of claims 82-85 wherein OMP85 is upregulated in one of the blebs.

87. The immunogenic composition of claims 82-86 wherein the blebs are isolated from meningococcal strains incapable of making capsular polysaccharide, preferably siaD⁻.
- 5 88. The immunogenic composition of claims 82-87 wherein the L2 and/or L3 LPS oligosaccharide structures are truncated consistent with the blebs having been isolated from meningococcal strains that are lgtB⁻.
- 10 89. The immiunogenic composition of claims 82-88 wherein the blebs are isolated from meningococcal strains that have downregulated expression of msbB.
90. The immunogenic composition of claims 82-89 wherein the L2 and/or L3 LPS oligosaccharide moieties are intra-bleb conjugated to outer-membrane proteins integral to the bleb.
- 15 91. The immunogenic composition of claims 82-90 wherein the blebs are derived from meningococcal strains which have downregulated expression of one or more of: FrpB, PorA, Opa or Opc.